Group IV: Claims 33-37, 78, and 79, drawn to murine ESX polypeptides;

Group V: Claims 38-45, drawn to anti- ESX antibodies;

Group VI: Claims 46-56, and 61-63, drawn to drawn to methods of detecting ESX dysregulation utilizing hybridization detection methods;

Group VII: Claims 46, 47, 49-54, and 57-60, drawn to methods of detecting ESX dysregulation utilizing antibody-based detection methods;

Group VIII: Claims 64-68, drawn to methods of inhibiting growth of a cell by utilizing an antisense nucleotide;

Group IX: Claims 64-65, and 69 drawn to methods of inhibiting growth of a cell by utilizing an antibody;

Group X: Claims 64-65, and 70 drawn to methods of inhibiting growth of a cell by utilizing an inactive ESX;

Group XI: Claims 72-76, drawn to transgenic animals;

Group XII: Claim 77, drawn to a method of determining whether a gene is regulated by an ESX polypeptide;

Group XIII: Claim 78, drawn to a pharmaceutical composition comprising an ESX nucleic acid;

Group XIV: Claim 80, drawn to a method of screening for a therapeutic lead compound;

Group XV: Claim 81, drawn to a method for identification of potential therapeutic targets.

In response to this restriction requirement, Applicants provisionally elect Group I, claims 1-15, 71 and 79, with traverse. Applicants explain below that the restriction between Groups VI and VII and between Groups VIII, IX, and X, respectively, is legally improper, the restriction between Groups I and II violates M.P.E.P. §803.04, and the restriction between the remaining groups is unnecessary.

The Restriction Between Groups VI and VII and Between Groups VIII, IX, and X is Legally Improper.

The restriction between Groups VI and VII and between Groups VIII, IX, and X, respectively, is legally improper because, in each case, the Examiner effectively requires that a single claim be divided up and presented in several applications. This flatly contravenes accepted law. As stated by the CCPA:

> As a general proposition, an applicant has a right to have ***each claim*** examined on the merits.
>
> * * *
>
> If, however, a single claim is required to be divided up and presented in several applications, that claim would never be considered on the merits. The totality of the resulting fragmentary claims would not necessarily be the equivalent of the original claim. Further, since the subgenera would be defined by the examiner, rather than by the applicant, it is not inconceivable that a number of the fragments would not be described in the specification.
>
> * * *
>
> §121 provides the Commissioner with the authority to promulgate rules designed to *restrict* an *application* to one of several claimed inventions, ... It does not provide a basis under the authority of the Commissioner to *reject* a particular *claim* on that same basis.
>
> * * *
>
> We hold that a rejection under §121 violates the basic right of the applicant to claim his invention as he chooses. *In Re Weber, Soder and Boksay* 198 USPQ 328, 331-332 (CCPA 1978)

See also, *In Re Haas* 179 USPQ 623, 624, 625 (*In Re Haas I*) and *In Re Haas* 198 USPQ 334-337 (*In Re Haas II*).

The CCPA thus recognized that an Examiner may not reject a particular claim on the basis that it represents "independent and distinct" inventions. *See, In re Weber Soder and Boksay, supra.* Moreover **the CCPA recognized that imposition f a restriction requirement on a single claim is just such an improper rejection.**

In particular, the courts have definitively ruled that the statute authorizing restriction practice, *i.e.*, 35 U.S.C. §121, provides no legal authority to impose a restriction requirement on a single claim, even if the claim presents multiple independently patentable inventions. *See, In Re Weber, Soder and Boksay, In Re Haas I, and In Re Haas II.* More specifically, the CCPA expressly ruled that there is no statutory basis for rejecting a claim for misjoinder, despite previous attempts by the Patent Office to fashion such a rejection. As noted in *Weber*:

> The discretionary power to limit one applicant to one invention is no excuse at all for refusing to examine a broad generic claim-- **no matter how broad, which means no matter how many independently patentable inventions may fall within it**. [emphasis added] *In Re Weber* at 334.

Applicants recognize that instead of improperly imposing a restriction requirement on a single claim, the Office may limit initial examination to a "reasonable number" of species encompassed by the claim. *See*, 37 C.F.R. §1.146. This practice strikes an appropriate balance between the concerns of the patent office regarding administrative concerns and unduly burdensome examination, and the clear constitutional and statutory rights of an inventor to claim an invention as it is contemplated, provided the dictates of 35 U.S.C. §112 are complied with. *See, e.g.,* the MPEP at 803.02, *In Re Wolfrum* 179 USPQ 620 (CCPA, 1973) and *In re Kuehl* 177 USPQ 250 (CCPA, 1973). Unlike a restriction requirement, a species election does not preclude an applicant from pursuing the original form of a claim in subsequent prosecution, nor does it force an applicant to file multiple divisional applications which are incapable of capturing the intended scope of the application. It should be clear that the added cost of filing and prosecuting 14 divisional patent applications in the present case does not strike an appropriate balance between the administrative concerns of the office and Applicants statutory rights as an inventor.

Finally, Applicants note that the CCPA has explicitly held that improper restriction of a single claim is a decision under the jurisdiction of the Board of Appeals, and the Federal Courts. This is in contrast to simple administrative decisions regarding ordinary

restriction requirements, which are not generally subject to Appellate review. *See, In Re Haas I, supra.* Because restriction of a single claim into multiple groups is tantamount to a rejection and a refusal to examine the claim as drafted, as articulated in *Haas I*, the Board of Appeals and the courts have jurisdiction over the decision. Accordingly, Applicants expressly reserve the right to appeal any decision that may be made regarding the present petition to the Patent Office Board of Appeals and to the Federal Circuit.

In view of the foregoing, Applicants have established that the restriction between Groups VI and VII and between Groups VIII, IX, and X, respectively, is legally improper and respectfully request that the restriction between these groups be withdrawn.

The Restriction Between Groups I and II Improperly Contravenes M.P.E.P. §803.04.

The restriction between Groups I and II improperly contravenes M.P.E.P. §803.04. The claims of Group I and Group II are drawn to human and murine ESX nucleic acids respectively. §803.04 expressly states that

> [T]o further aid the biotechnology industry in protecting its intellectual property without creating an undue burden on *the* Office, the Commissioner has decided *sua sponte* to partially waive the requirements of 37 C.F.R. 1.141 *et seq.* and permit a reasonable number of such nucleotide sequences to be claimed in a single application. See *Examination of Patent Applications Containing Nucletoide Squences* 1192 O.G. 68 (November 19, 1996)
>
> **It has been determined that normally ten sequences constitute a reasonable number o for examination pruposes.** [emphasis added] (MPEP §803.04)

The language of this section **is not** limited to Expressed Sequence Tags (ESTs). The language simply goes to "nucleotide sequences." There are far fewer than 10 nucleotide sequences in the present application. Accordingly, under MPEP §803.04, the restriction between Groups I and II should be withdrawn.

The restriction is unnecessary.

According to MPEP §803, the Examiner should examine all claims in an application, even though they are directed to distinct inventions, unless to do so would create a

serious burden. In the instant case, a proper search of human ESX polynucleotides would be expected to identify any prior art, if it exists, pertinent to murine ESX polynucleotides, human EXS polypeptides, and murine ESX polypeptides, and pharmaceutical compositions comprising an ESX nucleic acid. Accordingly, examination of Groups I, II, III, IV, and XIII together entails no greater burden than examination of one group alone and the restriction between Groups I, II, III, IV, and XIII should be withdrawn.

Examination of the remaining Groups with Groups I, II, III, IV, and XIII entails a search for art relevant to human and/or murine ESX. Again, the search for the remaining can be accomplished with essentially a single search. Examination of all of the Groups together entails no undue burden and the restriction requirement should be withdrawn.

In summary, Applicants note that the restriction between Groups VI and VII and between Groups VIII, IX, and X contravenes controlling law, is improper and should be withdrawn. The restriction between Groups I and II contravenes MPEP §803.04 and should be withdrawn. Finally examination of the Groups together, particularly Groups I, II, III, IV, and XIII entails no substantial burden and accordingly restriction between these groups should be withdrawn.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (415) 248-5500

Dated: June 23, 1999.

Respectfully submitted,

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APPENDIX I

CLAIMS PENDING IN 08/978,217

1. An isolated nucleic acid comprising a nucleotide sequence encoding at least about five contiguous amino acids of an ESX transcription factor variable region polypeptide, wherein said variable region has an amino acid sequence as set forth in SEQ ID NO: 7 or conservative substitutions of said amino acid sequence.

2. The isolated nucleic acid of claim 1, wherein said nucleic acid encodes an ESX transcription factor having an amino acid sequence as set forth in SEQ ID NO: 3.

3. The isolated nucleic acid of claim 2, wherein said nucleic acid has a nucleotide sequence as set forth in SEQ ID NO: 1.

4. The nucleic acid of claim 1, wherein said nucleic acid is amplified from a genomic library using the primer pairs designated by SEQ ID No. 13 and SEQ ID NO. 14.

5. The nucleic acid of claim 1, wherein said nucleic acid hybridizes to a clone of a human ESX gene under stringent conditions.

6. The nucleic acid of claim 1, wherein said nucleic acid further comprises a vector.

7. The nucleic acid of claim 1, wherein said variable region has an amino acid sequence as set forth in SEQ ID NO.: 7.

8. The isolated nucleic acid of claim 1, wherein said nucleotide sequence has a smallest sum probability of less than about 0.5 when compared to a nucleotide sequence as set forth in SEQ ID NO: 6 using a BLASTN algorithm using default parameters.

9. The isolated nucleic acid of claim 8, wherein said smallest sum probability is less than about 0.2.

10. An isolated nucleic acid comprising a label and a nucleotide sequence encoding a carboxy terminal domain of an ESX transcription factor, wherein said carboxy terminal domain has an amino acid sequence as set forth in SEQ ID NO: 12 or conservative substitutions of said amino acid sequence.

11. The nucleic acid of claim 10, wherein said nucleic acid is free of dideoxynucleotides.

12. The nucleic acid of claim 10, wherein said nucleic acid is single stranded.

13. The nucleic acid of claim 12, wherein said nucleic acid is a sense strand.

14. The isolated nucleic acid of claim 10, wherein said label is a radionuclide.

15. An isolated nucleic acid encoding a human ESX transcription factor polypeptide comprising at least 8 contiguous amino acids from a polypeptide sequence encoded by a nucleic acid as set forth in SEQ ID NO: 1, wherein:

said polypeptide, when presented as an antigen, elicits the production of an antibody that specifically binds to a polypeptide sequence encoded by a nucleic acid as set forth in SEQ ID NO: 1; and

said polypeptide does not bind to antisera raised against a polypeptide encoded by a nucleic acid sequence as set forth in SEQ ID NO: 1, that has been fully immunosorbed with a polypeptide encoded by a nucleic acid sequence as set forth in SEQ ID NO: 1.

16. An isolated nucleic acid comprising a nucleotide sequence encoding at least about ten contiguous amino acids of a murine ESX transcription factor polypeptide having an amino acid sequence as set forth as mESX in Figure 5 or conservative substitutions of said amino acid sequence.

17. The nucleic acid of claim 16, wherein said nucleic acid encodes an ESX transcription factor having an amino acid sequence as set forth as mESX in Figure 5.

18. The nucleic acid of claim 17, wherein said nucleic acid has a nucleotide sequence as set forth in SEQ ID NO: 15.

19. The nucleic acid of claim 16, wherein said nucleic acid is amplified from a genomic library using the primer pairs designated by SEQ ID No. 16 and SEQ ID NO. 17.

20. The nucleic acid of claim 16, wherein said nucleic acid hybridizes to a clone of a murine ESX gene under stringent conditions.

21. The nucleic acid of claim 16, wherein said nucleic acid further comprises a vector.

22. The nucleic acid of claim 16, wherein said nucleic acid is labeled.

23. The nucleic acid of claim 22, wherein said nucleic acid is free of dideoxynucleotides.

24. The nucleic acid of claim 22, wherein said nucleic acid is single stranded.

25. The nucleic acid of claim 24, wherein said nucleic acid is a sense strand.

26. The isolated nucleic acid of claim 22, wherein said label is a radionuclide.

27. An isolated nucleic acid encoding a murine ESX transcription factor polypeptide comprising at least 8 contiguous amino acids from a polypeptide shown as MESX in Figure 5, wherein:

said polypeptide, when presented as an antigen, elicits the production of an antibody that specifically binds to the polypeptide designated mESX in Figure 5; and

said polypeptide does not bind to antisera raised against the polypeptide designated mESX in Figure 5, that has been fully immunosorbed with the polypeptide designated mESX in Figure 5.

28. An isolated human ESX polypeptide, said polypeptide comprising a subsequence of at least 5 contiguous amino acids of a polypeptide encoded by a nucleic acid selected from the group consisting of SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:9, and SEQ ID NO:11, or conservative substitutions of said polypeptide subsequence.

29. The polypeptide of claim 28, wherein said polypeptide comprises a subsequence of at least 50 contiguous amino acids encoded by a nucleic acid selected from the group consisting of SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:9, and SEQ ID NO:11, or conservative substitutions of said polypeptide subsequence.

30. The polypeptide of claim 29, wherein said polypeptide is a polypeptide encoded by a nucleic acid selected from the group consisting of SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:9, and SEQ ID NO:11.

31. An isolated human ESX polypeptide, said polypeptide comprising at least 8 contiguous amino acids from a polypeptide sequence encoded by a nucleic acid as set forth in SEQ ID NO: 1, wherein:

said polypeptide, when presented as an antigen, elicits the production of an antibody which specifically binds to a polypeptide encoded by a nucleic acid as set forth in SEQ ID NO: 1; and

said polypeptide does not bind to antisera raised against a polypeptide encoded by a nucleic acid sequence as set forth in SEQ ID NO: 1 which has been fully immunosorbed with a polypeptide encoded by a nucleic acid sequence as set forth in SEQ ID NO: 1

32. The isolated polypeptide of claim 31, wherein said polypeptide is encoded by a nucleic acid as set forth in SEQ ID NO: 1.

33. An isolated murine ESX polypeptide, said polypeptide comprising a subsequence of at least 10 contiguous amino acids of the polypeptide designated mESX in Figure 5, or conservative substitutions of said subsequence.

34. The polypeptide of claim 33, wherein said polypeptide comprises a subsequence of at least 50 contiguous amino acids of the polypeptide designated mESX in Figure 5, or conservative substitutions of said polypeptide subsequence.

35. The polypeptide of claim 33, wherein said polypeptide is a polypeptide having the sequence of the polypeptide designated mESX in Figure 5.

36. An isolated murine ESX polypeptide, said polypeptide comprising at least 8 contiguous amino acids from the polypeptide sequence designated mESX in Figure 5, wherein:

said polypeptide, when presented as an antigen, elicits the production of an antibody which specifically binds to a polypeptide having the sequence designated mESX in Figure 5; and

said polypeptide does not bind to antisera raised against a polypeptide having the sequence designated mESX in Figure 5 which has been fully immunosorbed with a polypeptide having the sequence designated mESX in Figure 5.

37. The polypeptide of claim 36, wherein said polypeptide has the amino acid sequence designated mESX in Figure 5.

38. An anti-human ESX antibody which specifically binds to a polypeptide comprising at least 10 contiguous amino acids from a polypeptide encoded by a nucleic acid as set forth in SEQ ID NO: 1, wherein:

said polypeptide, when presented as an antigen, elicits the production of an antibody which specifically binds to a polypeptide encoded by a nucleic acid as set forth in SEQ ID NO: 1; and

said polypeptide does not bind to antisera raised against a polypeptide encoded by a nucleic acid sequence as set forth in SEQ ID NO: 1 which has been fully immunosorbed with a polypeptide encoded by a nucleic acid sequence as set forth in SEQ ID NO: 1.

39. The antibody of claim 38, wherein said polypeptide comprises 16 contiguous amino acids are encoded by a nucleotide sequence as set forth in SEQ ID NO:11.

40. The antibody of claim 38, wherein said antibody is monoclonal antibody.

41. A recombinant cell expressing the anti-human ESX antibody of claim 38.

42. An anti-human ESX antibody which specifically binds to a polypeptide comprising at least 10 contiguous amino acids from a polypeptide encoded by a nucleic acid as set forth in SEQ ID NO: 1, wherein:

said polypeptide, when presented as an antigen, elicits the production of an antibody which specifically binds to a polypeptide encoded by a nucleic acid as set forth in SEQ ID NO: 1; and

said polypeptide does not bind to antisera raised against a polypeptide encoded by a nucleic acid sequence as set forth in SEQ ID NO: 1 which has been fully immunosorbed with a polypeptide encoded by a nucleic acid sequence as set forth in SEQ ID NO: 1.

43. The antibody of claim 42, wherein said polypeptide comprises 16 contiguous amino acids are encoded by a nucleotide sequence as set forth in SEQ ID NO:11.

44. The antibody of claim 42, wherein said antibody is monoclonal antibody.

45. A recombinant cell expressing the anti-human ESX antibody of claim 42.

46. A method of detecting dysregulation of an ESX gene in an organism, said method comprising the steps of

i) providing a biological sample of said organism; and

ii) determining whether an ESX gene in said sample is expressed at a higher level or is present at a greater copy number compared to an ESX gene in a corresponding tissue known to be healthy.

47. The method of claim 46, wherein said dysregulation is a result of ESX gene amplification in cells of said sample.

48. The method of claim 47, wherein said gene amplification is detected by comparative genomic hybridization or FISH.

49. The method of claim 46, wherein said dysregulation is a result of ESX gene rearrangement in cells of said sample.

50. The method of claim 46, wherein expression of said ESX gene at a level at least 50% greater in said biological sample than in said healthy tissue is indicative of an epithelial cancer

51. The method of claim 46, wherein said epithelial cancer is human breast cancer.

52. The method of claim 51, wherein said healthy tissue comprises normal human mammary epithelial cells.

53. The method of claim 46, wherein abnormal expression of said ESX gene is indicative of an unfavorable prognosis.

54. The method of claim 46, wherein said method further comprises selecting an appropriate treatment regime.

55. The method of claim 46, wherein said detecting comprises detecting an ESX nucleic acid.

56. The method of claim 55, wherein said detecting comprises a hybridization assay.

57. The method of claim 46, wherein said detecting comprises detecting an ESX polypeptide.

58. The method of claim 57, wherein said detecting comprises an immunoassay.

59. The method of claim 58, wherein said ESX polypeptide is detected using an antibody which specifically binds a polypeptide comprising at least 10 contiguous amino acids from a polypeptide encoded by a nucleic acid as set forth in SEQ ID NO: 1.

60. The method of claim 59, wherein said nucleic acid is selected from the group consisting of SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:9, and SEQ ID NO:11.

61. A method of diagnosing an epithelial cancer in a patient, said method comprising:

contacting a nucleic acid sample from the patient with a probe which hybridizes selectively to a target polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:9, and SEQ ID NO:11 wherein the probe is contacted with the sample under conditions in which the probe hybridizes selectively with the target polynucleotide sequence to form a stable hybridization complex; and

detecting the formation of a hybridization complex.

62. The method of claim 61, wherein the nucleic acid sample is from a patient with breast cancer.

63. The method of claim 61, wherein the nucleic acid sample is a metaphase spread or a interphase nucleus.

64. A method of inhibiting growth or proliferation of neoplastic cells, said method comprising administering to said cells an effective amount of an agent that inhibits biological activity of an ESX transcription factor.

65. The method of claim 64, wherein said neoplastic cells comprise a cancer in an organism.

66. The method of claim 64, wherein said agent inhibits expression of said ESX transcription factor.

67. The method of claim 66, wherein said method comprises transfecting cells of said mammal with vector expressing an antisense ESX nucleic acid.

68. The method of claim 66, wherein said method comprises administering to said organism a therapeutically effective dose of a composition comprising an antisense ESX nucleic acid and a pharmacological excipient.

69. The method of claim 64, wherein said agent is an antibody that specifically binds said ESX transcription factor.

70. The method of claim 64, wherein said agent is an inactive ESX transcription factor mutein.

71. A transfected cell comprising a heterologous gene encoding an ESX transcription factor.

72. The transfected cell of claim 71, wherein said cell comprises a transgenic non-human animal.

73. The transgenic non-human animal of claim 72, wherein said animal comprises a mutated ESX transcription factor gene and said animal is deficient in ESX transcription factor activity.

74. The transgenic non-human animal of claim 73, wherein said deficiency is a result of a reduced level of ESX mRNA compared to an unmutated ESX gene in a similar milieu.

75. The transgenic non-human animal of claim 73, wherein said deficiency is a result of said mutated gene encoding an ESX polypeptide having a reduced level of biological activity compared to a wild-type ESX polypeptide.

76. The transgenic non-human animal of claim 73, wherein said mutated gene comprises one or more mutations selected from the group consisting of a missense mutation, a nonsense mutation, an insertion, or a deletion.

77. A method of determining whether a gene is regulated by an ESX polypeptide, said method comprising the steps of:

a) contacting a nucleic acid comprising a 5' flanking region of said gene with an ESX polypeptide to form a nucleic acid-protein complex;

b) treating said complex with a DNase under conditions sufficient to digest said nucleic acid at hypersensitive regions;

c) separating said DNase-treated complex to obtain a footprint pattern; and

d) determining whether said footprint pattern comprises a hypersensitive band flanked by two protected regions, wherein said hypersensitive band corresponding to a first guanine residue in a GGA sequence is indicative of said gene being regulated by an ESX polypeptide.

78. A pharmacological composition comprising a pharmaceutically acceptable carrier and a molecule selected from the group consisting of consisting of a vector encoding an ESX nucleic acid or subsequence thereof, an ESX polypeptide or subsequence thereof, and an anti-ESX antibody.

79. A kit for the detection of a ESX gene or polypeptide, said kit comprising a container containing a molecule selected from the group consisting of an ESX nucleic acid or subsequence thereof, an ESX polypeptide or subsequence thereof, and an anti-ESX antibody.

80. A method of screening for a therapeutic lead compound, said method comprising the steps of:

(i) providing a nucleic acid encoding a polypeptide of ESX exon 4 or a polypeptide sequence of ESX exon 4;

(ii) contacting said nucleic acid or said polypeptide sequence with said compound; and

(iii) detecting binding of said compound to said nucleic acid or said polypeptide sequence.

81. A method of identifying potential therapeutic targets for drug screening, said method comprising the steps of:

i) identifying a subsequence of the ESX gene or protein necessary for ESX transactivational activity;

ii) performing a nucleic acid or protein database search to identify other nucleic acids having significant sequence identity with said subsequence whereby said subsequence is identified as a potential therapeutic target for drug screening.